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Vasoactive therapy in shock

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Learning objectives

By reading this article you should be able to:

- Outline the pathophysiology of shock and goals of therapy.
- Classify vasopressors based on their pharmacological properties and clinical actions.
- Summarise the important clinical trials of vasopressors.
- Discuss the pathophysiology of specific shock states and choose the appropriate vasopressor for a given clinical setting.

Key points

- Septic shock is the most common type of shock.
- Multimodal assessment of myocardial function and the state of the systemic and pulmonary vasculature should guide the choice of vasopressor therapy.
- Noradrenaline (norepinephrine) is the recommended first-line agent in septic shock.
- Vasopressor therapy should be individualised to the predominant subtype of shock and adapted to dynamic changes in pathophysiology.
- Dynamic arterial elastance and biomarker-guided vasopressor therapy hold promise for the future.

A thorough understanding of vasoactive drugs is mandatory for any clinician managing patients in shock. There are different types of shock, but the initial therapy is often generic. This review details the pharmacology, clinical use and specific application of vasopressor therapies in the various types of shock. We also propose an algorithm to help guide bedside management outlining a stepwise approach in various types of shock. Details of fluid therapy, inotropic agents and mechanical circulatory support are beyond the scope of the review, as is cardiac output (CO) monitoring.

Definition of shock

Shock is best defined as a life-threatening, generalised form of acute circulatory failure associated with inadequate oxygen utilisation by the cells.[1] The cornerstone of therapy is emergent restoration of critical oxygen delivery.

Four distinct pathophysiological types of shock have been described in adults—distributive, cardiogenic, hypovolaemic and obstructive. Although easier to describe each as a distinct clinical entity, it is not uncommon for subtypes to coexist. Septic shock is the most common form of shock encountered in the ICU, followed by cardiogenic and hypovolaemic shock, with obstructive shock being relatively rare. ICU and in-hospital mortality from septic shock is reportedly as high as 35% and 40%, respectively.[2] Therefore, it is paramount that this life-threatening emergency is diagnosed and treated promptly. In order to optimise outcomes, a treatment 'bundle' has been recommended in the management of shock.[2]

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Pathophysiology of shock

Systemic hypotension can result from a variety of pathophysiological mechanisms. These include reduced venous return; afterload reduction; obstruction to pulmonary or systemic blood flow; reduced CO; or a varying combination of these.

Venous return is the flow of blood from the periphery back to the right atrium. The main determinants of venous return are the vascular system compliance, the circulating volume, venous resistance and right atrial pressure (RAP). In order for flow to occur, there must be a pressure gradient. This is the gradient between the mean systemic filling pressure (MSFP) and RAP, along which blood flows. The main determinants of MSFP are the circulating volume and venous tone. A decrease in circulating volume or an increase in venous resistance will reduce venous return. Venous return is equal to CO, hence a reduction in venous return will lead to a decrease in stroke volume (SV). At steady state, SV is the main determinant of arterial pulse pressure by causing arterial distension, the degree of which is proportional to the arterial elastance (Ea). A decrease in SV will therefore produce a decrease in BP. A reduction in vascular tone also causes systemic hypotension. In health, LV end-systolic elastance and Ea are well matched to provide optimal ventriculo-arterial coupling. Both arterial tone and MSFP are difficult to measure at the bedside; hence surrogates are used to assess a patient's haemodynamic profile. These include arterial pressure, central venous pressure, SV, oxygen consumption, lactate and the arteriovenous carbon dioxide gap.

In shock, various mechanisms mediate the loss of vasomotor tone that leads to systemic hypotension. Down-regulation of $ß_1$ and $ß_2$ receptors leads to a blunted response of resistance vessels to noradrenaline (norepinephrine). The endothelium itself plays an important role in regulating its reactivity through two ubiquitous molecules—nitric oxide (NO) and prostacyclin. Increased production of inducible NO synthase and prostacyclin occurs in response to bacterial endotoxin and proinflammatory cytokines. Increased production of these molecules contributes to vasodilation in shock. In addition, profound vasodilatation with vasopressin deficiency leads to refractory hypotension.[3] Septic shock can cause left ventricular dilatation, depressed systolic and diastolic function with delayed recovery after 8–10 days.

Management of shock

Time is of the essence in the management of shock; hence diagnosis and treatment should occur together. Intravascular volume resuscitation should be commenced immediately, with a thorough assessment to guide vasoactive therapy. A full cardiovascular assessment should include assessment of cardiac systolic function, loading condition of the ventricles, systemic and pulmonary vascular tone and tissue perfusion (Fig. 1). Elucidation of the predominant type of shock with cardiovascular profiling will allow individualisation of fluid and vasoactive support, restoration of oxygen supply and metabolism (Fig. 2). Right ventricular failure as a single entity or in conjunction with other types of shock should be part of the initial cardiovascular evaluation.[4]

Classification of vasopressors

The site of action, usual dose, indication and major adverse effects of vasopressors in clinical use are summarised in Table 1.

Noradrenaline

Noradrenaline is a sympathomimetic catecholamine and an important endogenous neurotransmitter. Its effects are mediated mainly through $α_1$-adrenergic receptors causing vascular smooth muscle contraction in both the systemic and pulmonary vasculature. It also has modest activity at $α_2$-, $ß_1$-and $ß_2$-adrenergic receptors, producing weak positive inotropic and chronotropic effects. Noradrenaline causes α-mediated constriction of the splanchnic circulation, thereby augmenting stressed volume.[5] This augmentation of stressed volume increases the systemic driving pressure (MSFP-RAP) with little effect on the HR and CO. Noradrenaline is the first-line vasoactive drug for the treatment of septic shock.[2] The incidences of tachycardia, hyperlactataemia and hyperglycaemia are lower in patients treated with noradrenaline compared with those treated with adrenaline (epinephrine).[6] There is an increased rate of atrial fibrillation when compared with vasopressin.[7] In the early phases of shock, noradrenaline may improve cardiac performance because of better ventriculo-arterial coupling, increased coronary perfusion and weak ß-mediated inotropic effects.[8]

Adrenaline

Adrenaline is a sympathomimetic catecholamine, endogenous hormone and neurotransmitter produced by the adrenal glands and to a lesser extent in the CNS. It has a higher affinity to ß than α receptors, which is dose dependent. At low doses (0.01–0.1 μg kg^{-1} min^{-1}) it mainly stimulates ß receptors resulting in positive inotropy and chronotropy. At higher doses (>0.1 μg kg^{-1} min^{-1}) there is an increased action on vascular smooth muscle, producing increased vascular resistance and arterial BP on responsive vessels.[9] Adrenaline also has strong metabolic effects. It decreases insulin secretion, stimulates glycogenolysis, glycolysis and lipolysis. This can lead to a high catabolic rate, hyperglycaemia and raised lactate concentrations, and tachyarrhythmias and possible cardiac and splanchnic ischaemia. Multiple RCTs and meta-analyses have failed to show a difference in mortality from septic shock when compared with using single agent noradrenaline,[6] or to a combination of noradrenaline with vasopressin or dobutamine.[10–12] It is recommended as a second-line agent for septic shock because of its adverse effect profile. Adrenaline prevents mast cell degranulation via effects on mast cell ß2 receptors, resulting in reduced histamine and prostaglandin release. Consequently, it is the first-line agent in management of anaphylaxis.[13] Adrenaline is also the drug of choice in cardiac arrest.[14]

Phenylephrine

Phenylephrine is a synthetic catecholamine. It is less potent but has a longer half-life than noradrenaline. Phenylephrine can be used as an i.v. bolus or as a continuous infusion. It is a popular vasopressor agent in anaesthesia and may be used during early resuscitation to maintain perfusion pressure. Its use is not well investigated in vasodilatory shock and it can cause marked reduction of CO, secondary to $α_1$-mediated systemic and splanchnic vasoconstriction.[15] A retrospective before/after observational cohort study in septic shock was associated with higher mortality in comparison with noradrenaline.[16]

Metaraminol

Metaraminol is an $α_1$ agonist that also stimulates noradrenaline release. Metaraminol has a short half-life and can be

Myocardial function	Vasomotor tone/ fluid responsiveness	End-organ perfusion
• TTE/TOE • Transpulmonary thermodilution - PAC, PiCCO, LiDCO	• Dynamic fluid responsiveness • SVR • Transpulmonary thermodilution	• Mentation • Urine output • Mottling of skin • Lactate/metabolic status • $Svo_2/Scvo_2$ • CO_2 gap

Fig 1 Tools to evaluate cardiovascular profile in shock. PAC, pulmonary artery catheter, PiCCO, pulse contour cardiac output; $Scvo_2$, central venous oxygen saturation; Svo_2, mixed venous oxygen saturation; SVR, systemic vascular resistance; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiogram.

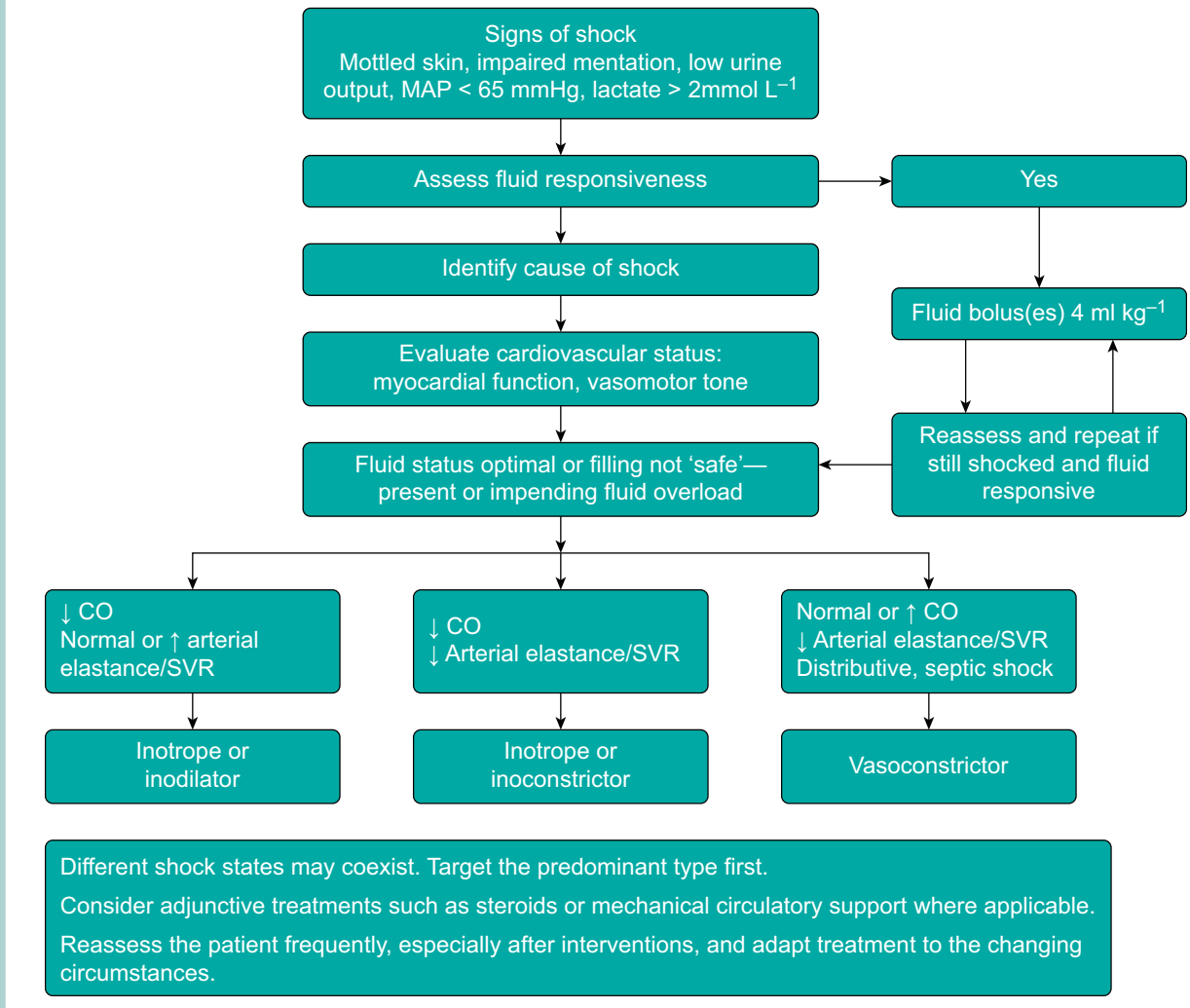
Signs of shock
Mottled skin, impaired mentation, low urine output, MAP < 65 mmHg, lactate > 2mmol L−1
Assess fluid responsiveness
Yes
Identify cause of shock
Fluid bolus(es) 4 ml kg−1
Evaluate cardiovascular status: myocardial function, vasomotor tone
Reassess and repeat if still shocked and fluid responsive
Fluid status optimal or filling not 'safe'— present or impending fluid overload
↓ CO
Normal or ↑ arterial elastance/SVR
↓ CO
↓ Arterial elastance/SVR
Normal or ↑ CO
↓ Arterial elastance/SVR
Distributive, septic shock
Inotrope or inodilator
Inotrope or inoconstrictor
Vasoconstrictor
Different shock states may coexist. Target the predominant type first.
Consider adjunctive treatments such as steroids or mechanical circulatory support where applicable.
Reassess the patient frequently, especially after interventions, and adapt treatment to the changing circumstances.

Fig 2 Algorithm for use of vasoactive therapy in shock. SVR, systemic vascular resistance.

given peripherally. It can cause reflex bradycardia, but small observational studies suggest that it has effects similar to phenylephrine on the cardiovascular system. It is mainly used perioperatively for hypotension as an i.v. bolus. It can be given as a continuous infusion when central access is not available. High-quality data in the ICU are limited.

Table 1 Vasopressors in clinical use. cGMP, cyclic guanosine monophosphate

	Drug	Site of action	Usual dose	Indication	Major adverse effects
Catecholamines	Noradrenaline	Strong α_1 and modest ß	0.01–0.5 μg kg^{-1} min^{-1}	First-line in septic shock	- Tachyarrhythmias - Severe peripheral/ visceral ischaemia
	Adrenaline	ß: 0.01–0.1 μg kg^{-1} min^{-1} α_1: >0.1 μg kg^{-1} min^{-1}	0.01–0.3 μg kg^{-1} min^{-1}	Cardiogenic shock Vasodilatory shock Cardiac arrest Severe bradycardia	- Tachyarrhythmias - High glucose/lactate - Severe peripheral/ visceral ischaemia
	Phenylephrine	Strong α_1	0.4–4 μg kg^{-1} min^{-1}	Hypotension	- Reflex bradycardia - Severe peripheral/ visceral ischaemia
	Metaraminol	Strong α_1: stimulates noradrenaline release	boluses of 0.5–1 mg	Hypotension secondary to vasodilation	- Reflex bradycardia - Severe peripheral/ visceral ischaemia
	Dopamine	$D_{1,2}$: 1–5 μg kg^{-1} min^{-1} ß: 5–10 μg kg^{-1} min^{-1} α_1: 10–15 μg kg^{-1} min^{-1}	1–15 μg kg^{-1} min^{-1}	Vasodilatory shock Severe bradycardia	- Tachyarrhythmias - Severe peripheral/ visceral ischaemia - Immunosuppression
Non-catecholamines	Vasopressin	V_{1a}, V_{1b}, V_2	0.01–0.04 U min^{-1}	Second-line in septic shock	- Severe peripheral/ visceral Ischaemia
	Terlipressin	V_{1a} (V_{1b}) > V_2	Infusion 20–160 μg h^{-1} or boluses 1–2 mg q.d.s	Vasodilatory shock Acute liver failure	- Severe peripheral/ visceral ischaemia
	Angiotensin II	AT_1, AT_2	5–200 ng kg^{-1} min^{-1}	Vasodilatory shock	- Tachyarrhythmias - Severe peripheral/ visceral ischaemia
	Methylene blue	cGMP blocker	bolus 2 mg kg^{-1}, infusion 0.2–2 mg kg^{-1} h^{-1}	Vasodilatory shock	- Falsely low Spo_2 readings - Methaemoglobinaemia - Pulmonary vasoconstriction

Dopamine

Dopamine is a sympathomimetic catecholamine, endogenous hormone and neurotransmitter produced by the CNS and the kidneys. Dopamine binds α_1, $ß_1$, $ß_2$ and dopaminergic D_1 and D_2 receptors. It causes splanchnic and renal vasodilation and augments natriuresis and urine output, but has no role in the recovery of renal function in patients with acute kidney injury (AKI).[17] Increasing doses produce a positive inotropic effect with eventual vasoconstriction. Besides the high rate of severe tachyarrhythmias in the SOAP II trial, dopamine may induce pituitary dysfunction. Compared with noradrenaline, a recent meta-analysis demonstrated a higher mortality and morbidity.[17,18] It is recommended that dopamine is used only in highly selected cases where bradycardia is the mechanism of shock. Use of dopamine to improve renal perfusion or to treat AKI is not recommended.[2]

Vasopressin

Vasopressin is a peptide hormone produced in the hypothalamus and released into the circulation as arginine vasopressin in response to high plasma osmolarity. It is a potent vasoconstrictor, stimulates adrenocorticotropic hormone release and induces platelet aggregation and release of coagulation factors. It binds V_{1a}, V_{1b} and V_2 receptors. Vasopressin increases water reabsorption in the renal collecting ducts via its action on V_2 receptors. It increases systemic vascular resistance, augmenting arterial and coronary perfusion pressure, via V_{1a} receptors. It does not increase pulmonary vascular resistance. Vasopressin and its analogues can potentially cause peripheral and visceral ischaemia. The relative vasopressin deficiency seen in sepsis, coupled with its synergy with noradrenaline, make vasopressin a useful vasopressor in sepsis and septic shock.[2,7,19] A *post hoc* analysis of the VASST trial suggested that early vasopressin therapy may reduce kidney injury in patients who are at risk of AKI.[20] Furthermore, the VANCS trial showed that the composite outcome of death or major complications after cardiac surgery favours vasopressin over noradrenaline. This positive result was mainly driven by a lower complication rate (fewer incidences of tachycardia and AKI) rather than a mortality benefit. A large meta-analysis confirmed a lower incidence of tachyarrhythmias but a higher rate of digital ischaemia with vasopressin uses versus any other vasoactive agent in septic shock.[21] The Surviving Sepsis Guideline (SSC) recommends vasopressin as a second-line agent to noradrenaline for septic shock.[2]

The synthetic analogues terlipressin and selepressin have higher affinity to V_{1a} receptors causing more vasoconstriction and less antidiuretic effect. Selepressin has recently been studied in two phase II and III trials. These failed to show any benefit when compared with noradrenaline. In a randomised, multicentre trial there was no difference in mortality between the terlipressin and noradrenaline groups, with a higher incidence of adverse effects in the terlipressin group.[22]

Angiotensin II

Angiotensin II (is a novel molecule derived from angiotensin I by action of angiotensin converting enzyme. Renin, which is secreted by the kidneys, converts angiotensinogen to angiotensin I. Angiotensin II binds to AT_1 and AT_2 receptors. Effects include profound vasoconstriction, increased aldosterone synthesis and vasopressin release. The phase III angiotensin II trial ATHOS-3 showed marked MAP elevation and noradrenaline-sparing effects, with the adverse event profile similar to noradrenaline.[23] Given that the ATHOS-3 trial was only powered for increases in MAP, further high-quality, large-scale studies are needed.

Methylene blue

Methylene blue inhibits NO-induced guanylate cyclase activation, thereby preventing smooth muscle relaxation. Methylene blue increases MAP and decreases noradrenaline requirements in sepsis and after cardiotomy.[24] No large scale RCT has investigated the role of methylene blue in shock. Methylene blue may absorb emitted light leading to a falsely low oxygen saturation reading. Other adverse effects include methaemoglobinaemia and pulmonary vasoconstriction.

Specific shock states

Distributive/septic shock

Distributive shock is characterised by excessive vasodilatation (reduction in vasomotor tone), reduced BP and relatively preserved cardiac contractility. Septic shock is the most common form of distributive shock.

Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities occur and is associated with a greater risk of mortality than with sepsis alone.[25] Optimising end organ perfusion remains the cornerstone of therapy. Intravascular volume and tone may have to be restored to improve stressed volume and venous return.

Septic shock can be described as a triad of vasodilatation, relative hypovolaemia and myocardial depression. Whilst optimising tissue oxygen delivery is the overarching goal, specific elements may need to be manipulated individually. There invariably tends to be a degree of overlap, with one element being more predominant. The contribution of each element to the shock state may not be clear, therefore use of dynamic measures of fluid responsiveness and CO monitoring can be useful to examine the cardiovascular profile. Echocardiography is an invaluable tool that provides a global assessment of the cardiovascular system which can be repeated to assess the response to an intervention. This will allow individualisation of therapy, especially after initial empirical treatment. Vasoconstrictors should be used after optimisation of circulating volume. Positive inotropic agents should only be used when myocardial depression predominates.

RCTs have examined commonly used vasopressors to evaluate their effect on mortality and relevant secondary outcomes in septic shock (Table 2).

The Surviving Sepsis Campaign guideline recommends restoration of intravascular volume within the first 3 h, based on individualised measurement of fluid responsiveness.[2] It also advocates early use of vasopressors to achieve systemic perfusion pressure. Noradrenaline is recommended as the first-line vasopressor for management of septic shock.

The term refractory septic shock represents a condition at the severe end of the septic shock spectrum. Although lacking consensus, it is generally defined as end-organ dysfunction, hypotension requiring high-dose vasopressor drugs, usually at a dose of $>0.5\ \mu g\ kg^{-1}\ min^{-1}$ of noradrenaline or equivalent. It carries an extremely high mortality.[26] Vasopressin or adrenaline should be considered in cases of refractory shock with escalating doses of noradrenaline to achieve the recommended target MAP of 65 mmHg, or to decrease the dose of noradrenaline.[2] Corticosteroid treatment is suggested if adequate fluid resuscitation and vasopressor therapy are unable to restore haemodynamic stability.[2]

Cardiogenic shock

The recently proposed definition of cardiogenic shock by the Society for Cardiovascular Angiography and Interventions[27] describes cardiogenic shock as a dynamic continuum of clinical severity from the at-risk category to cardiac arrest refractory to traditional resuscitation efforts. Prompt recognition and treatment may potentially prevent progression of, and indeed reverse cardiogenic shock.

Acute myocardial infarction with left ventricular dysfunction is the most common cause of cardiogenic shock. Although coronary reperfusion, where indicated, remains the standard of care, a strategy comprising vasoactive therapy with or without inotropic support is often necessary. Myocardial dysfunction is inevitably present in patients with cardiogenic shock, but it is imperative to assess the vasomotor tone. Maintaining coronary perfusion and adequate venous return are the goals of therapy. After a thorough assessment of cardiac function, preload optimisation and inotropic drugs are indicated. Vasopressor drugs should be titrated cautiously against cardiovascular measurements as increasing afterload may have a detrimental effect on SV if contractility remains poor. Inotropic agents may also be harmful by increasing HR and myocardial oxygen demand. Although in theory the CO could be increased by a high HR, tachycardia compromises diastolic filling thereby reducing CO. Coronary perfusion time is also decreased. This may lead to myocardial ischaemia, further perpetuating the shocked state.

Treatment using a combination of inoconstrictors and inodilators has been associated with a lower short-term mortality in severe cardiogenic shock compared with using inoconstrictors such as adrenaline alone. Dobutamine is recommended as the first-line inotropic agent with levosimendan as the second choice.[28]

Obstructive shock

Obstructive shock is said to exist when there is mechanical obstruction that limits CO. This may result from either intra- or extramural occlusion of the large vessels (central pulmonary embolism, inferior vena cava syndrome), the heart (cardiac tamponade) or a critical increase in intrathoracic pressure (tension pneumothorax, dynamic hyperinflation). Features may mimic other forms of shock, but the condition requires prompt recognition and alleviation of the precipitating factor. Treatment depends on the specific aetiology which can be elusive and may resemble other form(s) of shock, particularly cardiogenic shock. The pathophysiology is typically

Table 2 Landmark RCTs of vasoactive agents. LOS, length of stay, PO, primary outcome; RRT, renal replacement therapy; SAE, sepsis associated encephalopathy; SIRS, systemic inflammatory response syndrome; SO, secondary outcome; SOFA, sequential organ failure assessment.

Trial	Year	Intervention	Control	Primary outcome	Secondary outcome	Findings
SEPSIS -ACT	2019	Selepressin	Placebo	Ventilator- and vasopressor-free days up to Day 30	90-day mortality, 30-day ICU, RRT-free days	No difference in primary and secondary outcomes
ATHOS 3	2017	Angiotensin II	Placebo	Predefined increase in MAP at 3 h	Change in SOFA, mortality, change in vasopressor dose	Significantly higher percentage of patients achieving PO. Cardiovascular SOFA significantly lower in treatment group
VANISH	2016	Noradrenaline	Vasopressin	AKI-free days	Mortality, RRT, SAE	No difference in PO, less RRT in vasopressin group
SOAP II	2010	Noradrenaline	Dopamine	28-day mortality	ICU, hospital LOS, organ support-free days, time to attainment of haemodynamic stability, changes in haemodynamic variables, use of inotropes	No difference in PO, dopamine associated with more arrhythmias, increased risk of death in cardiogenic shock
VASST	2008	Noradrenaline	Vasopressin	28-day mortality	90-day mortality; days alive and free of organ dysfunction, ventilator/ vasopressor/RRT/ SIRS/corticosteroid-free days/LOS/SAE	No difference in PO/ no difference in SAE
CAT	2008	Adrenaline	Noradrenaline	Achieving MAP goal for >24 h without pressors	28- And 90-day mortality	No difference in PO, SO
CATS	2007	Adrenaline	Noradrenaline	28-Day mortality	Mortality at Day 7, 14, 90, ICU/hospital discharge, systemic haemodynamics, arterial pH and, lactate; SOFA, time to haemodynamic success, vasopressor withdrawal	No difference in PO/ SO

characterised by high afterload or low preload, or a combination of the two to varying degrees. A low CO state rapidly ensues, manifesting as tissue hypoperfusion in the form of oliguria, altered mentation and increased lactate. Imaging of the cardiovascular system is often helpful with echocardiography often providing vital diagnostic information.

The immediate goal of therapy is to alleviate the obstruction and restore CO. Vasoactive agents may need to be used in an attempt to maintain tissue oxygen delivery whilst definitive treatment is achieved. Noradrenaline may increase right ventricular inotropy by improving coronary perfusion and can be considered in the setting of obstructive shock secondary to pulmonary embolism.[29] This should be weighed against the risk of further increasing systemic vascular resistance with careful consideration of individualised haemodynamics.

Hypovolaemic shock

The primary goal of treatment in hypovolaemic shock is to restore circulating volume. Vasopressors have a limited role and can be used as a holding measure whilst intravascular

volume is restored. Emergency control of ongoing bleeding, when present, is pivotal to resuscitation. Ongoing volume losses should be mitigated for resuscitation to be effective. When circulating volume has been optimised, noradrenaline is generally recommended as the vasopressor of choice, whilst dobutamine or adrenaline is recommended for inotropic support in the presence of myocardial dysfunction. Early use of vasopressors in the resuscitation of haemorrhagic shock after trauma is potentially associated with increased mortality.

Future directions

As we understand more and more about the physiology of shock, we may move away from phenotype-driven classification towards precision medicine. The concept of 'broad spectrum vasopressors' has been suggested to mimic the natural response of the body to poor perfusion states by using multiple pathways simultaneously, not just a single catecholamine as a first-line agent.[30] The initial mixed vasopressor 'cocktail' then would be assessed, and non-beneficial ones would be stopped as appropriate, in a way similar to antibiotic therapy. Another approach is to use more sensitive monitoring to assess arterial tone with surrogate bedside measurements such as dynamic arterial elastance (Ea_{dyn}). Ea_{dyn} is the ratio between arterial pulse pressure and SV changes during respiration, which appears to be a useful tool that can predict vasopressor need.[31] Others believe that biomarkers will be able to guide our decision on vasopressor choice.[24] As with other aspects of medicine, it is likely that artificial intelligence will become the main tool guiding vasopressor choice. By processing large amounts of complex information, closed-loop systems could potentially guide this aspect of ICU therapy.

Declarations of interest

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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